decisions regarding the safety of environmental chemicals. Testing the high priority chemicals is critical to achieving the overall NTP goal of protecting public health by preventing exposures and generating the data that can make risk assessments more reliable. Abstracts of NTP study results and other NTP data and information are also available through the Internet, a relatively recent development which has greatly expanded dissemination of NTP information (see adjoining story).

There are no restrictions on chemical nominations; they may focus on individual chemicals, classes of chemicals, or broad public health issues. Nominations may be made for studies that will 1) identify chemical hazards, 2) improve the risk assessment process, 3) test hypotheses of mechanisms of action, 4) reduce the number of animals needed for toxicity/carcinogenicity evaluations, or 5) lead to new mechanistically based short-term tests.

The more information presented in a chemical nomination, the stronger the nomination. It is essential that specific and substantive reasons why a chemical should be studied are given. If possible, the nomination should contain the Chemical Abstracts Service (CAS) number of the chemical, especially if it has more than one name. CAS numbers can be obtained from *The Merck Index,* available in the reference sections of most public and university libraries. Information on the volume of chemical manufactured or in use and information on its uses is also helpful. A bibliography of any previous research is valuable, including animal and other laboratory studies, epidemiological studies, and medical case studies.

However, even if little or none of this background information is available, nominations will still be considered. Every letter of nomination will receive a response. Letters nominating chemicals and supporting information should be sent to:

Chemical Nomination Office c/o Errol Zeiger MD A2-02, NIEHS, PO Box 12233, Research Triangle Park, NC 27709 USA.

Nomination Principles for NTP Studies

The NTP Executive Committee operates under the principle that industry will evaluate chemicals or other agents for health and environmental effects as intended and mandated by the Congress under legislative authorities. The NTP, acting under its nomination principles, will solicit nominations for NTP studies from the following categories:

1. Chemicals found in the environment that are not closely associated with a single commercial organization;
2. Biological or physical agents that may not be adequately evaluated without federal involvement;
3. Commercial chemicals with significant exposure that were first marketed before current testing requirements or those that generate too little revenue to support further evaluations;
4. Potential substitutes for existing chemicals or drugs that might not be developed without federal involvement;
5. Substances that occur as mixtures for which evaluations cannot be required of industry;
6. Chemicals or agents that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities;
7. Chemicals that should be evaluated to improve the scientific understanding of structure–activity relationships and thereby help limit the number of chemicals requiring extensive evaluations;
8. Emergencies or other events that warrant immediate government evaluation of a chemical or agent.

The NTP will assess the specific needs for studies, evaluate existing literature and testing data, assess ongoing evaluations in the government and private sector, and also determine how the chemical fits into an overall plan for improving the test systems before committing to specific studies. The selection of a chemical or agent by the NTP Executive Committee does not automatically commit the NTP to evaluate that chemical or agent. The priority of the chemicals and the proposed studies are assessed during the selection of contractors to conduct the studies. During any of these phases the chemical or study may be withdrawn if higher priority studies are found, or if the study proves to be impractical.

NTP to Study 22 Chemicals

The following chemicals are being considered for short- and long-term toxicology and carcinogenesis studies. The NTP welcomes comments on these chemicals and relevant information including ongoing toxicological studies, current or future trends in production and import, use patterns, human exposure levels, environmental occurrence, and toxicological data.

Contact may be made by mail to: William Eastin, NIEHS/NTP, PO Box 12233, Research Triangle Park, NC 27709, by telephone (919) 541-7941, FAX (919) 541-4714, or E-mail at Eastin@NIEHS. NIH.GOV.

Riddelliine (CAS no. 23246-96-0). Two-year studies via oral gavage in B6C3F$_1$ mice and F344 rats. Riddelliine is a pyrrolizidine alkaloid found in plants of the genus *Senecio* in the western United States. Riddelliine and other alkaloids in these plants can cause the death of livestock if ingested in high quantities, or may contaminate meat as a residue. Riddelliine may also contaminate commercial grains, milk, and honey, and is found in some herbal teas. In NTP 90-day studies riddelliine was found to cause hepatic toxicity in mice and rats and hepatic neoplasia in rats. Two-year carcinogenicity studies of standard design are proposed to determine the shape of the dose–response curve for carcinogenicity in rats, and further evaluate the toxic and carcinogenic potential in mice.

Urethane/ethanol mixture (CAS no. 51-79-6/64-17-5). Two-year studies via dosed-water in B6C3F$_1$ mice and F344 rats. Urethane and ethanol are byproducts of fermentation and are commonly found in alcoholic beverages and in many foods. Urethane has been recognized as a rodent and nonhuman primate carcinogen, while the International Agency for Research on Cancer has determined that alcoholic beverages are human carcinogens. Two-year studies that are planned will include separate groups of male and female mice exposed to urethane (CAS no. 51-79-6), ethanol (CAS no. 64-17-5), or to several levels of urethane and ethanol in the drinking water. The studies will include an assessment of the toxicokinetics of urethane, with and without ethanol, following repeated dosing. Studies of urethane DNA adducts are planned to address the issue of the dosimetry of DNA alterations.

Dichlorodiphenyl sulfone (CAS No. 80-07-9). Two-year studies via dosed-feed in B6C3F$_1$ mice and F344 rats. Dichlorodiphenyl sulfone is a component of high temperature plastics. A known inducer of cytochrome P450s, dichlorodiphenyl sulfone was shown to cause marked hepatomegaly in NTP prechronic studies. Other studies have shown facile oral absorption and a relatively simple metabolite pattern, as well as self induction of metabolism with repeated administration. Carcinogenicity studies with dichlorodiphenyl sulfone are planned with both sexes of rats and mice.

Elmiron (CAS no. 37319-17-8). Fourteen-day studies via oral gavage in B6C3F$_1$

mice and F344 rats. Elmiron is a pentosan polysulfate used as an experimental drug in the United States for the treatment of interstitial cystitis and used in Europe to prevent thrombosis and hyperlipidemia. The U.S. FDA nominated elmiron to the NTP as an "orphan" drug in need of chronic toxicity and carcinogenicity evaluation. Currently, 14-day studies are being undertaken to determine if expected effects on the clotting system will be the basis on which to select doses for further evaluations. Chronic toxicity and carcinogenicity evaluations by standard designs are under consideration.

Benzophenone (CAS no. 119-61-9). Two-year studies via dosed-feed in $B6C3F_1$ mice and F344 rats. Benzophenone is found in many consumer products, e.g., as a fragrance and flavor enhancer, photoinitiator, ultraviolet curing agent, a polymerization inhibitor, and in the manufacture of pesticides and various pharmaceuticals. In NTP 13-week studies, the oral administration of benzophenone was found to cause hepatocellular hypertrophy in rats and mice and evidence of cholestatic liver injury and renal damage in rats. Marked induction of hepatic CYP 450 IIB was observed in rats and mice. Chronic toxicity and carcinogenicity studies are proposed for this chemical, with a stop exposure group using a dose which produced marked liver and kidney lesions in prechronic studies. Toxicokinetic studies are also planned.

2-Hydroxy-4-methoxybenzophenone (CAS no. 131-57-7). Two-year studies via dosed-feed in $B6C3F_1$ mice and F344 rats. 2-Hydroxy-4-methoxybenzophenone is a UV stabilizer used in cosmetic, pharmaceutical, and plastic products. In NTP 13-week studies by the oral and topical routes, similar sites of toxicity were seen, primarily the liver and kidney, and effects on sperm density and the length of the estrous cycle were noted. Two-year studies of standard design are planned for this chemical by the oral route of administration.

Methacrylonitrile (CAS no. 126-98-7). Two-year studies via oral gavage in $B6C3F_1$ mice and F344 rats. Methacrylonitrile is an industrial chemical widely used in a variety of organic processes related to the manufacture of polymers. It is a highly reactive unsaturated aliphatic nitrile found in cigarette smoke and is known to liberate cyanide *in vivo*. Methacrylonitrile has been studied extensively by the NTP including 14-day and 90-day studies in rats and mice by gavage. In addition, absorption, disposition, toxicokinetics, cell proliferation, and developmental toxicity studies have been performed. This chemical will be the subject of modeling efforts with physiologically based pharmacokinetic modeling techniques and is also recommended for 2-year chronic toxicity and carcinogenicity studies of a standard design.

Acrylonitrile (CAS no. 107-13-1). Two-year studies via oral gavage in $B6C3F_1$ mice and F344 rats. Acrylonitrile is extensively used for the manufacture of synthetic fibers, resins, elastomers, rubber and plastics. There is limited evidence for the carcinogenicity of acrylonitrile in workers and it has been shown to produce chromosome damage in the blood cells of exposed workers. Acrylonitrile has produced brain, stomach, and zymbal gland tumors in 2-year studies in rats, but has not been studied in mice. Clues to critical metabolites may be gained from comparative studies in mice. Therefore, acrylonitrile will be studied in mice by the standard NTP protocol. Toxicokinetic estimates will be derived by analysis of an acrylonitrile-glutathione conjugation product in the urine.

***m*-Nitrotoluene** (CAS no. 99-08-1). Two-year studies via dosed-feed in $B6C3F_1$ mice and F344 rats. The nitrotoluenes are high production volume chemicals used in the synthesis of agricultural and rubber chemicals and in various dyes. There are differences in the patterns of metabolism of nitrotoluenes. The *ortho*-isomer undergoes a series of microflora-mediated reactions leading to an intermediate with high capacity to bind to hepatic DNA and induce unscheduled DNA synthesis. In extensive NTP prechronic studies an unexpected finding was the presence of chemically induced mesothelioma in male rats receiving *o*-nitrotoluene. Studies demonstrated that microflora metabolism was not necessary for the mesothelioma response. Chronic toxicity and carcinogenicity studies are planned with *o*-nitrotoluene (CAS no. 88-72-2) and *p*-nitrotoluene (CAS no. 99-99-0), as well as *m*-nitrotoluene.

***m*-Cresol** (CAS no. 108-39-4). Two-year studies via dosed-feed in $B6C3F_1$ mice and F344 rats. The cresols are monomethyl derivatives of phenol, and are found as constituents of coal tar, in various industrial solvents and resins, and in some essential oils. There are no adequate chronic toxicity and carcinogenicity studies of the cresols. The NTP has performed comparative 13-week toxicity studies in rats and mice by the dosed feed route. The isomers were found to exhibit generally similar patterns of toxicities, with the *o*-isomer (CAS no. 95-48-7) being somewhat less toxic than *m*- or *p*-cresol (CAS no. 106-44-5). Comparative chronic toxicity and carcinogenicity studies in rats and mice are planned for the cresols.

2,4-Decadienal (CAS no. 25152-84-5). Thirteen-week and 2-year studies via oral gavage in $B6C3F_1$ mice and F344 rats. 2,4-Decadienal is one of the class of dienaldehydes that occur naturally in a variety of foods as by-products of the peroxidation of polyunsaturated lipids. Ingested lipid oxidation products and oxidized fats have been reported to cause damage to the liver and kidneys, increased cellular proliferation in the gastrointestinal tract, and other nonspecific tissue injury. Several researchers have suggested a possible link between lipid peroxidation products in the diet and human cancer. 2,4-Decadienal, as well as 2,4-hexadienal (CAS no. 142-83-6), will be studied in prechronic and chronic toxicity and carcinogenicity studies in rats and mice.

Dipropylene glycol (CAS no. 25265-71-8). Two-year studies via dosed-water in $B6C3F_1$ mice and F344 rats. Dipropylene glycol is a component of antifreeze, air fresheners/sanitizers and is used as a stabilizer in cosmetics, as a component in polyester, alkyd resins, plastics, as a plasticizer and as a solvent. It was found to be of low to moderate toxicity in NTP 13-week studies. Mortality, hepatocellular lesions including atypical foci and an adenoma were seen in rats at the highest dose. Findings in mice were limited to increased liver weights. Carcinogenicity studies of a standard design are proposed for dipropylene glycol.

Arsenic trioxide (CAS no. 1327-53-3). (Study plans are being formulated.) Arsenic trioxide is a by-product of copper or lead smelting operations and is used in pesticides, in the manufacture of glass, pharmaceuticals and other industrial chemicals. Arsenic and arsenic compounds have been classified as human carcinogens by IARC, Arsenic is a common water contaminant and there is need for information on biomarkers of exposure for low dose risk estimations. Specific study designs are under development.

Tamoxifen (CAS no. 10540-29-1). (Conjugated estrogens study plans are being formulated.) Conjugated estrogens are listed by IARC as human carcinogens causing endometrial cancer. Estrogens are prescribed for prevention of osteoporosis in post-menopausal women and are used as oral contraceptives. Tamoxifen is a mixed estrogen agonist/ antagonist known to be effective in the treatment and prevention of estrogen sensitive breast cancer. Tamoxifen also causes endometrial cancer in humans. Studies are being designed to help characterize dose-response relationships and cancer risks for estrogen agonist and antagonists.

MX [3-Chloro-4-(dichloromethyl)-5-hydroxy-2-furanone] (CAS no. 77439-76-0). (Study plans are being formulated.) MX is a mutagenic by-product of water and wood pulp chlorination and has been determined to account for about half of the mutagenic potency of finished drinking water. The EPA has nominated MX for carcinogenicity studies with the expectation that the outcome could influence U.S. drinking water contaminant standards. Study designs are incomplete.

Erratum

In the article "MCS: A Sensitive Issue" (volume 102, no. 9, pp. 746–750), the name of the president of the National Center for Environmental Health Strategies, Mary Lamielle, was misspelled. We sincerely apologize for this error.